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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/838,858

04/20/2001

S. Gary Mansfield

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04/08/2005

EXAMINER

EPPS FORD, JANET L

ARENT FOX KINTER PLOTKIN & KAHN PLLC - NEW YORK
C/O MARGARET P. DROSOS, DIRECTOR OF IP ADMIN.
1050 CONNECTICUT AVENUE, NW
WASHINGTON, DC 20036-5339

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/838,858

Applicant(s)

MANSFIELD ET AL.

Examiner

Janet L. Epps-Ford, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 September 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 35-79 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 35-72, 74, 75 and 77-79 is/are rejected.
- 7) ☒ Claim(s) 73 and 76 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 8-25-04.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

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DETAILED ACTION

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application; the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 USC § 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Specifically, there is no support for a target binding domain that targets binding to a non-human factor VIII pre-mRNA, or a nucleotide sequence to be trans-spliced to the target pre-mRNA wherein said nucleotide sequence encodes a factor VIII polypeptide. Therefore, claims 35-79 will be afforded a priority date of April 20, 2001.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). See page 3 of the specification filed 1-02-2002, wherein the Post Office Address of Hengjun Chao was altered, however the alteration was not initialed and/or dated.

Specification

3. The abstract of the disclosure is objected to because the following informalities. At least pages 2, 8, 25, and 31 contain editor's markings. Applicant should provide a clean copy of the specification. Appropriate correction is required. See MPEP § 608.01(b).

Claim Objections

4. Claims 73 and 76 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim (a) in the case of claim 73, cannot depend from any other multiple dependent claim; (b) in the case of claim 76, should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims 73 and 76 have not been further treated on the merits.

5. Claims 43, 56, and 64 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 43 fails to further limit claim 35, and claim 56 fails to further limit claim 50. Claim 64 fails to further limit claims 57-60.

Response to Arguments

6. Applicant's arguments with respect to claims 1-34 have been considered but are moot in view of Applicant's cancellation of these claims. The following new ground(s) of rejection are directed to the newly submitted claims.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 79 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 79 recites the limitation "the viral vector of claim 37" in line 1. There is insufficient antecedent basis for this limitation in the claim, because claim 37 is drawn to a cell comprising a nucleic acid molecule, and does not recite a viral vector.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 35-72, 74-75, and 77-79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

The instant claims have been amended to recite cells comprising a nucleic acid molecules, expression vectors comprising said nucleic acid molecules and methods of producing a chimeric nucleic acid molecule comprising the use of said nucleic acid molecules, and nucleic acid molecules. The instant claims recite wherein said nucleic acid molecules comprise a nucleotide sequence to be trans-spliced to a target pre-mRNA wherein said nucleotide sequence

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encodes a factor VIII polypeptide. The claims recite wherein said nucleic acid molecules comprise target binding domains that target binding of the nucleic acid molecule to a non-human factor VIII pre-mRNA, a 3' and/or 5' splice region, a spacer region, and further comprising a nucleotide sequence sufficient to encode a full-length factor VIII polypeptide. The scope of the newly added claims, now encompass nucleotide sequences including *human sequences* that encode factor VIII polypeptide to be trans-spliced to *non-human* factor VIII pre-mRNA.

Moreover, the phrase "non-human" is not supported by the specification as filed. Although, Applicants describe nucleic acid comprising target binding domains that target binding of the nucleic acid molecule to a mouse factor VIII pre-mRNA, there is no support for target domains that target binding to any other non-human form of factor VIII other than the mouse factor VIII pre-mRNA. Applicant's amendment is considered new matter since the specification as filed does not provide adequate support for the full scope of the presently claimed invention, since a generic or subgeneric disclosure cannot support a species unless the species is specifically described in the specification as filed. (See MPEP § 2163.05 [R-2]).

11. Claims 35-56 and 74-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: making a transgenic mouse whose somatic and germ cells comprise the nucleic acid molecules as recited in the instant claims, does not reasonably provide enablement for any transgenic animal comprising an exogenous nucleic acid encoding any target pre-mRNA or comprising pre-trans-splicing molecule, method of making an transgenic animal or method of using any transgenic animal for producing chimeric RNA molecule as broadly encompassed by the claimed invention. The specification does not enable

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any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

In the instant case, the claimed invention encompasses making and using any transgenic mouse comprising any exogenous nucleic acid comprising any targeting sequence and at least one consensus splice site, or acceptor site. However the specification as filed does not provide sufficient guidance for practicing the claimed invention commensurate with the full scope of the claims and the art of transgenesis is unpredictable. An artisan of skill would have required

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specific guidance for modifying a method used in mouse to make and use any transgenic animal and due to the unpredictability of the state of the art of transgenesis an artisan of skill would have required undue experimentation to make and use the claimed invention commensurate with the full scope of the claims as discussed below.

As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. Introduction of foreign DNA into fertilized oocyte, for example by micro injection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the non-human mammals species will be highly variable and unpredictable. Even if the transgenic animals are produced, it is highly unpredictable whether transgenic animals from species other than mouse (in the present case) will express the transgene to a level high enough so as to enable the development of the claimed phenotype in the transgenic animals. Investigators observed 5-70 fold lower yields of a recombinant protein in transgenic mice when they used a construct designed for expression in sheep (see lines 1-12 in 4th para of col 1 on page 632 in Mullins et al. (Mullins JJ et al. Hypertension 22:630-633,1993)). The variation in expression levels between different cell lines and species may be attributed to host genetic background, the site of chromosomal insertion and absence of specific transcription factors.

In a more recent assessment of the transgenic technology, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, "[W]ell regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in non-targeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

For example, Hammer et al. (Hammer RE et al. Cell 63:1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 micro-globulin. Although, both the transgenic animals bearing HLA-b27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rats demonstrated most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in widely different phenotypic responses even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been functional in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype. If not, what steps would have been taken to address this issue? It is

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noted that while the cited articles were published in 1997 or before, the issues that need to be addressed for using a technique used in mouse for using in making any other animal remain the same. For example, Smith (Journal of Biotechnology 99: 1-22, 2002) reviewed the state of the art of gene transfer in higher animals and discussed the same problems. In addition to the problems discussed above, Smith noted that the use of ES cells is limited because to date only mouse ES cells could be unequivocally be established.

In addition to the general problems discussed above, the claimed invention is not enabled by the instant specification because of lack of specific guidance for several claimed limitations. For example, the instant claims recite one or more target binding domains in the target pre-mRNA, which encompasses any sequence however, there is no evidence that sequences except intron sequences of a gene of interest could be used. The specification at page 21 states that "[A]s used herein, a target binding domain is defined as any sequence that confers specificity of binding and anchors the pre-mRNA closely in space so that the spliceosome processing machinery of the nucleus can trans-splice a portion of the PTM to a portion of the pre-mRNA." However, this description does not provide any specific characteristics of the binding domain that would confer specific binding and anchor the pre-mRNA in the splicing machinery for processing. Next, the claim recites a nucleotide that is to be trans-spliced to the target pre-mRNA. Again the specification does not provide specific guidance regarding the structure of the sequence that could be spliced to the target pre-mRNA, except that exon sequence may comprise a translatable protein capable of producing a reporter molecule. This indicates that the nucleotide sequence to be trans-spliced is an exon, and the specification does not teach any sequence or what other sequence could be used.

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In view of the above, the specification fails to provide sufficient guidance for an artisan of skill to have made the claimed invention commensurate with the full scope of the claims and an artisan of skill would have required undue experimentation to practice the claimed invention because the state of the art of the invention was unpredictable and therefore, limiting the scope of the claimed invention as discussed above is proper.

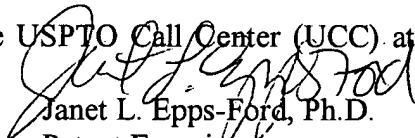
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.


Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1635

JLE